UNIT 13

Organic Synthesis

A2 Level
Chemistry
Notes

Topics

Unit 13: Organic Synthesis

13.1: Synthesis of Chiral Drug Molecules

Designing New Medicinal Drugs:

How do we go about designing new molecules to fight diseases? One way is to identify the structural features the new drug will need to stop particular bacteria or viruses working. The structural features may be associated with the active site on a particular enzyme needed for an essential function of the pathogen. Once these structural features have been identified we can then predict the shape of a molecule that would fit into, and hence block, the active site.

The functional groups present would also be crucial to ensure the drug could bind into the active site effectively.

The intermolecular bonds formed between the drug and its target molecule could involve:

- hydrogen bonding
- ionic attraction
- dipole–dipole forces
- instantaneous dipole–induced dipole forces (van der Waals' forces).

Computers are now used to judge the fit between a potential drug molecule and a receptor site on its target molecule. Such **molecular modelling** has greatly speeded up the process of designing new medicines. The interactions and fit of a potential medicine with a biological receptor molecule can be

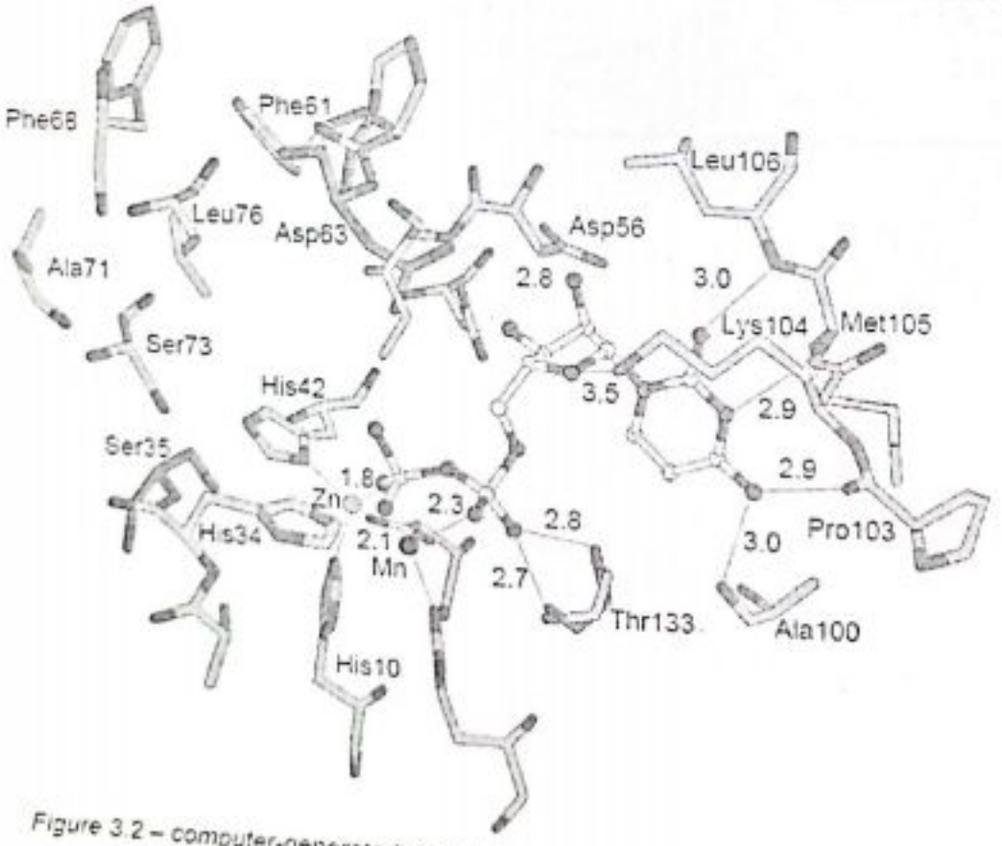


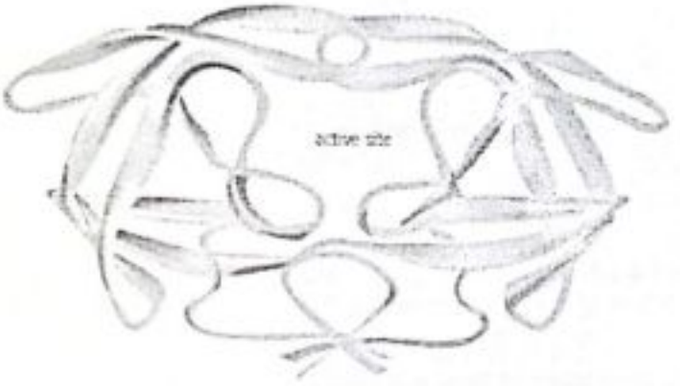
Figure 3.2 – computer-generated model of a drug in the active site of an enzyme, showing hydrogen bonds

studied before the medicine is ever made in the lab. Before molecular modelling became available, the synthesis of a new medicine involved far more trial and error. Chemists had to prepare many more possible medicines for testing.

With molecular modelling, only those molecules that are definite possibilities are made and tested. Molecular modelling on a computer is now a powerful tool, used when designing medicines and many other compounds (e.g. pesticides and polymers).

This type of research was used in the fight against AIDS in the late 1980s and 1990s. Scientists using X-ray crystallography (a method in which a sample is irradiated with X-rays and the pattern is analysed by computer) worked out the shape of HIV protease in 1988. This enzyme plays an important role when the virus becomes infectious. Researchers realized that, if a molecule could be discovered that could block its active site, this might be one step on the route to finding a cure for AIDS. Knowing the molecule that the enzyme worked on (its substrate), researchers were able construct similar molecules on the computer screen to fit the active site.

The first attempts fitted perfectly, but were not water soluble. This meant the drug could not be delivered to its target, the HIV protease. Eventually a soluble molecule that would interfere with the enzyme was found. In less than 8 years pharmaceutical companies had developed three new anti-viral drugs for people with HIV/AIDS.



This would have taken about twice as long if the structure of HIV protease had not been determined. Traditional trial-and-error methods involve the testing of many thousands of possible drugs. The death rate from AIDS dropped significantly. However, the virus developed resistance to the new drugs as it mutated. So scientists now have to model the new drug-resistant strains of the infection and are developing new drugs to inhibit the mutant versions of HIV protease. These inhibitors are one part of a cocktail of drugs that can be used to treat the disease now.

Identifying Macromolecules:

NMR spectroscopy is also used extensively in finding out the structures of biological macromolecules such as proteins and nucleic acids. As well as identifying the different types of ^1H atoms present, more sophisticated data can yield, for example, the distance between atoms in macromolecules. Large amounts of data are collected and analysed by computer programs to reveal the shape of the molecules under investigation. Figures 30.3 and 30.4 show images obtained from NMR analysis of two protein molecules made up from over 100 amino acids. These are called **ribbon diagrams**

Ribbon diagrams of the protein molecules containing variable number of amino acids.

This NMR analysis takes place in solution, so it is particularly useful for medical research. Many human proteins exist in solution in the body so we can mimic the interactions that take place in cells or in the bloodstream.

Chirality in Pharmaceutical Synthesis:

The pharmaceutical industry is constantly searching for new drugs. Their research chemists have discovered that most of these drugs contain at least one chiral centre. Remember that a molecule containing a carbon atom bonded to four different atoms or groups of atoms can exist as two non-superimposable mirror images.

These two isomers are called enantiomers and they will be optically active. They differ in their ability to rotate the plane of polarised light to the left or to the right. Using conventional organic reactions to make the desired product will yield a 50 : 50 mixture of the two enantiomers. We call this a racemic mixture. Although the physical properties of the enantiomers will be identical, each differs in its 'pharmaceutical activity', i.e. the effect the drug has on the body.

For example, naproxen is a drug used to treat the pain caused by arthritis. One enantiomer will ease the pain but the other can cause liver damage. As another example, one enantiomer of a drug used to treat tuberculosis (TB) is effective, whereas the other can cause blindness. Therefore, chemists ideally need a single pure enantiomer to put in their drug product. Note that about 80% of new drugs patented are single enantiomers.

Using Pure Enantiomers will be Beneficial as it:

- reduces the patient's dosage by half as the pure enantiomer is more potent, i.e. has better therapeutic activity (thereby cutting costs of production)
- minimises the risk of side effects (thereby protecting patients from further problems and drugs companies from possible legal action for damages if serious side effects do occur).

There are three ways to prepare pure enantiomers:

1. optical resolution
2. using optically active starting materials
3. using a chiral catalyst.

Optical Resolution:

This method involves the chemists following a traditional synthetic route to make the compound, resulting in a racemic mixture. Then they separate the two enantiomers in a process called **optical resolution**.

This involves using a pure enantiomer of another optically active compound (called a chiral auxiliary) that will react with one of the isomers in the mixture. The new product formed will now have different properties and so can be separated by physical means. For example, the solubility in a given solvent will differ so the unwanted enantiomer and the new product can be separated by **fractional**

crystallisation. The new product is then converted back to the desired enantiomer in a simple reaction (e.g. by adding dilute alkali).

The crystallisation is repeated many times to ensure purity. This method is difficult, time-consuming, uses extra reagents and involves the disposal of half the original racemic mixture.

Large volumes of organic solvents (often harmful to the environment) are used in the process.

However, chemists are now using **supercritical carbon dioxide as a solvent**, which is much safer. At **31 °C and 73 atmospheres pressure, CO_2 is a suitable non-polar solvent** for many drug derivatives in the racemic resolution process. The solubility of the derivatives can be changed, simply by varying the density of the solvent. The solvent, which is non-toxic, is easily removed by reducing the pressure and then recycling it to use in the process again.

We can also use **high-performance liquid chromatography** to separate a racemic mixture, as long as the stationary medium (e.g. the solid that packs the column) is itself optically active.

Using Optically Active Starting Materials:

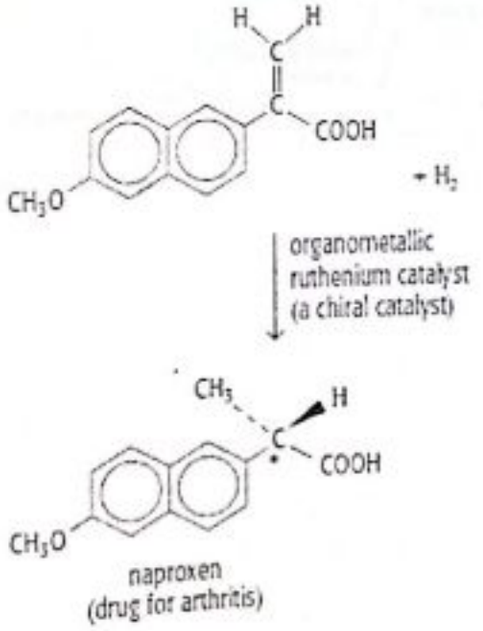
This technique uses starting materials that are themselves optically active and in the same orientation as the desired product. These are often **naturally occurring compounds** such as carbohydrates or L-amino acids. The biochemist will choose from this 'chiral pool'. The synthetic route is designed to keep any intermediates and the final product formed in the same enantiomeric form. As a result, there is no need to carry out the costly separation process needed when a racemic mixture is produced.

Chiral Catalysts:

Chemists are also developing new chiral catalysts that ensure only one specific enantiomer is formed in a reaction. The benefits of these catalysts are that only small quantities are needed and they can be used over and over again, although the catalyst itself can be expensive.

A ruthenium (Ru) organometallic catalyst is used in the production of naproxen. Often a combination of optical resolution and chiral synthesis is needed in the production of a pharmaceutically active, pure enantiomer.

The pharmaceutical industry can also use enzymes to promote stereo selectivity and produce single-enantiomer products. The specific shape and the nature of the molecular interactions at the active site of an enzyme ensure only one enantiomer will be formed (as in living things). The enzymes are often



naproxen
(drug for arthritis)

immobilised (fixed in place) on inert supports. This enables the reactants to be passed over them without the need to separate the product from the enzymes after the reaction.

However, it can be expensive isolating enzymes from living things. Using whole organisms, such as bacteria, can reduce this cost. Nowadays, synthetic enzymes can also be made, designed for a particular synthesis. Therefore a search for a suitable enzyme from the limited pool available from natural sources is not always necessary.

Overall, using an enzyme process might take longer to develop than a conventional synthetic route, but in the long run the benefits generally outweigh the disadvantages. There are fewer steps needed in the synthesis route, resulting in a 'greener' process.

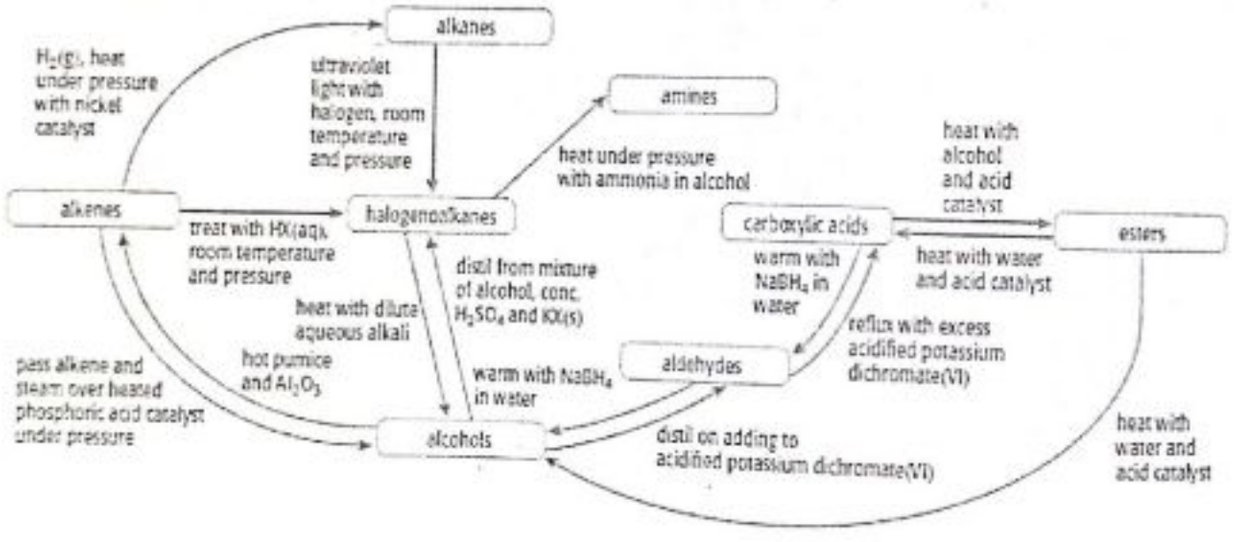
13.2: Synthetic Routes:

When research chemists want to make a new compound, they usually work backwards from the desired compound to create a series of reactions, starting with a compound extracted from a commonly available raw material. In industry, common starting materials are hydrocarbons from crude oil and its refining, and compounds extracted from plants, such as esters from fats and vegetable oils.

You will need some of the skills of a research chemist when tackling questions that involve:

- predicting the reactions of complex molecules you have never seen before, containing more than one functional group
- suggesting a series of reactions to make a given compound from a given starting compound.

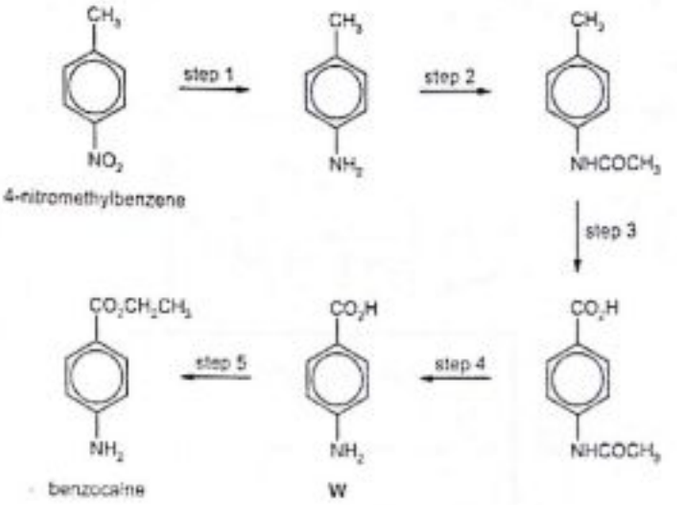
In order to be successful in answering these questions, you will need to be familiar with all the reactions and conditions of each homologous series mentioned in the syllabus. The flow chart in Figure is a summary of these reactions.



13.3: End of Chapter Past Paper Questions

Q1: O/N 17/P41/Q6, O/N 17/P43/Q6/b,e

(a) Benzocaine is used as a local anaesthetic. It can be synthesised from 4-nitromethylbenzene by the route shown.



(i) Give the systematic name of compound W.

..... **[1]**

(ii) Suggest the reagents and conditions for steps 1– 5.

step 1 .....

step 2 .....

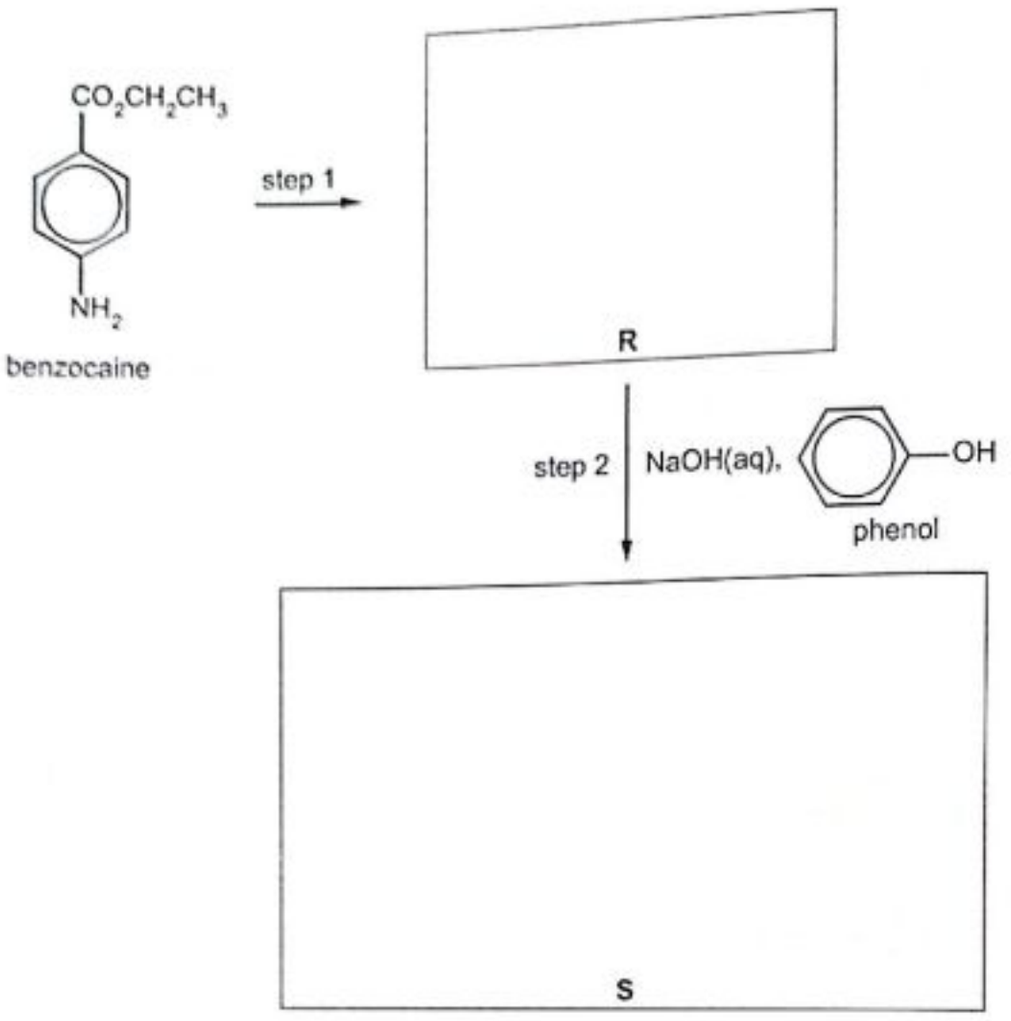
step 3 .....

step 4 .....

step 5 .....

[6]

(b) Benzocaine can also be used to synthesise the dyestuff S by the following route.



(i) Suggest the reagents used for step 1.

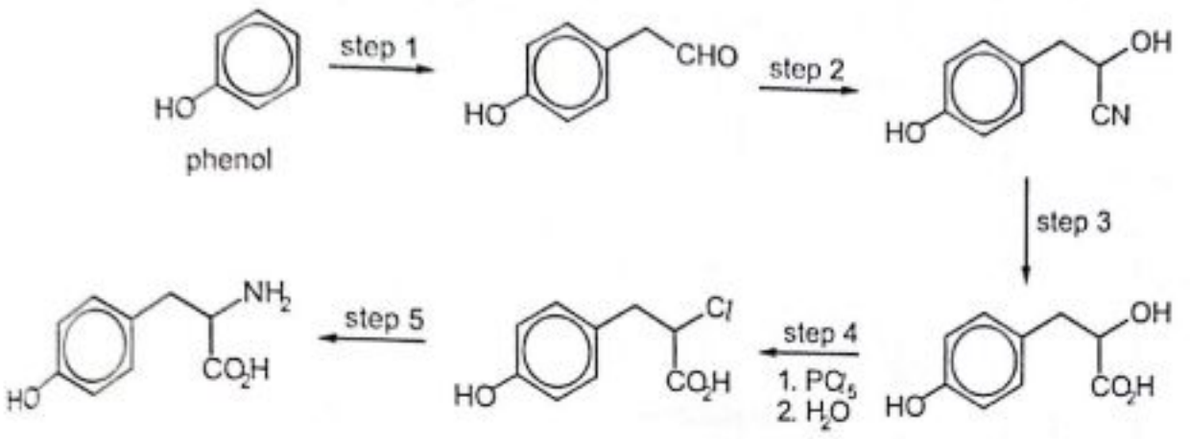
..... [1]

(ii) Suggest structures for compounds **R** and **S** and draw them in the boxes.

[2]

Q2: M/J 17/P42/Q8/a

(a) The amino acid tyrosine can be synthesised from phenol by the route shown.



(i) Name the mechanism occurring in the following steps.

step 1.....

step 2 .....

[2]

(ii) What *type of reaction* is occurring in step 3?

..... [1]

(iii) Suggest reagents and conditions for each of the following steps.

step 1 .....

step 2 .....

step 3 .....

step 5 .....

[5]

(iv) Draw the structures of the products of the reactions of tyrosine with an **excess** of each of the following reagents.

[4]

Q3: M/J 17/P41/Q4, M/J 17/P43/Q4

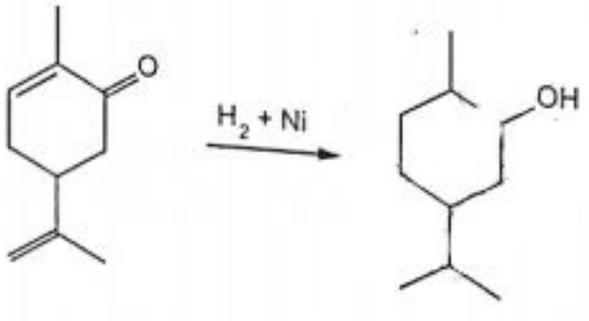
Carvone occurs in spearmint and a stereoisomer of carvone occurs in caraway seeds. Treating either isomer with hydrogen over a nickel catalyst produces a mixture of isomers with the structural formula

with NaOH(aq)

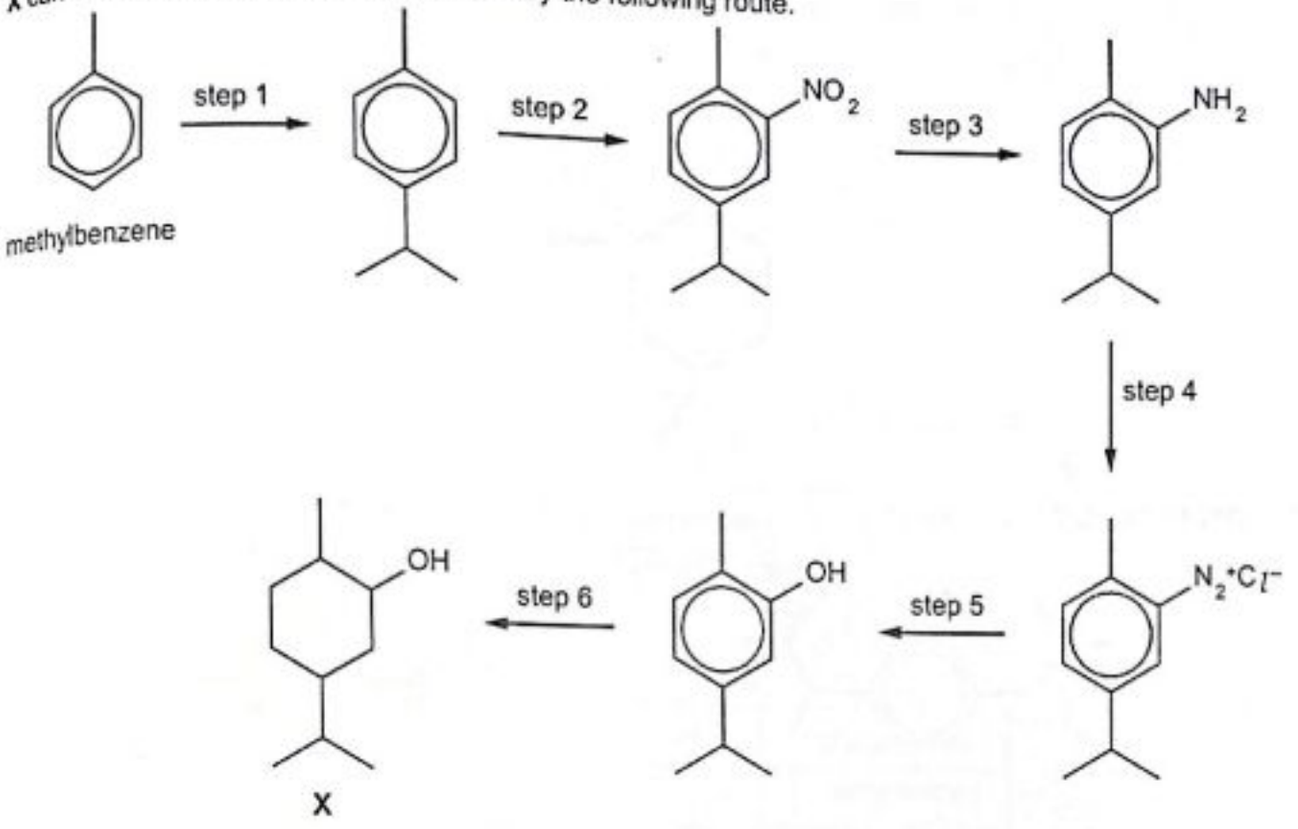
with HCl(aq)

with Br_2(aq)

X.



X can be synthesised from methylbenzene by the following route.



(b) (i) Name the mechanism in step 1.

..... [1]

(ii) What type of reaction is occuring in the following steps?

step 3.....

step 5.....

[2]

(iii) Suggest reagents and conditions for each of the following steps.

step 1.....

step 2.....

step 3.....

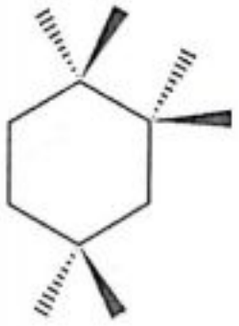
step 4.....[6]

(c) During step 6, hydrogen is added to the benzene ring to produce the cyclohexane ring in **X**.
The six hydrogen atoms are all added to the **same side** of the benzene ring.

(i) State the reagents and conditions needed for this reaction.

..... [1]

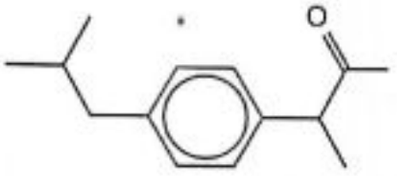
(ii) Complete the part structure to show the structure of the isomer of **X** that would most likely be obtained during this reaction.



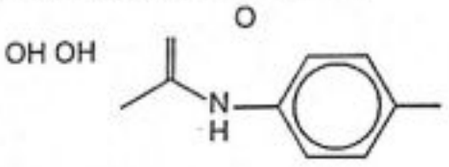
X

Q4: O/N 16/P41/6, O/N 16/P43/Q6

Ibuprofen and paracetamol are pain-relief drugs.



paracetamol



ibuprofen

(a) Ibuprofen and paracetamol both contain the aryl (benzene) functional group.
Name the **other** functional groups present in each molecule.

ibuprofen.....

paracetamol.....

[2]

(b) Ibuprofen contains a chiral centre and shows stereoisomerism.

(i) State what is meant by the term *chiral centre*.

.....

..... [1]

(ii) Draw the two stereoisomers of ibuprofen.

[2]

(c) Draw the structures of the organic products when ibuprofen and paracetamol react separately with $LiAlH_4$.

product with ibuprofen

product with paracetamol

(d) A student carried out some reactions with solutions of ibuprofen and paracetamol using reagents **D** and **E** and the following results were obtained.
(✓ means a reaction took place.)

reagent	ibuprofen	paracetamol
D	✓	✗
E	✗	✓

(i) Suggest a possible identity for each reagent **D** and **E**.

D .....

E .....

[2]

(ii) Give the structure of the organic product formed when reagent **D** reacted with ibuprofen.

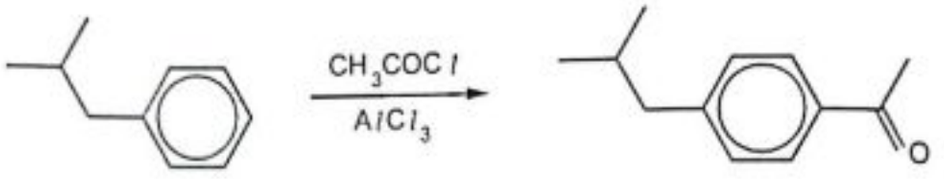
product with ibuprofen

[1]

(iii) Give the structure of the organic product formed when reagent **E** reacted with paracetamol.

product with paracetamol

(e) One of the steps in the manufacture of ibuprofen is shown.

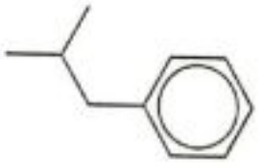


X Y

(i) Write an equation for the reaction between CH_3COCl and $AlCl_3$.

..... [1]

(ii) Complete the mechanism for the conversion of **X** into **Y**. Include all necessary curly arrows, any relevant dipoles and charges.



X

(iii) Name the mechanism in (ii).

..... [1]

Q5: M/J 15/P42/Q6

(a) Carboxylic acids can be converted into primary amines by the following sequence of reactions.

(i) Suggest the identity of intermediate **D** and write its structure in the box above. **[1]**

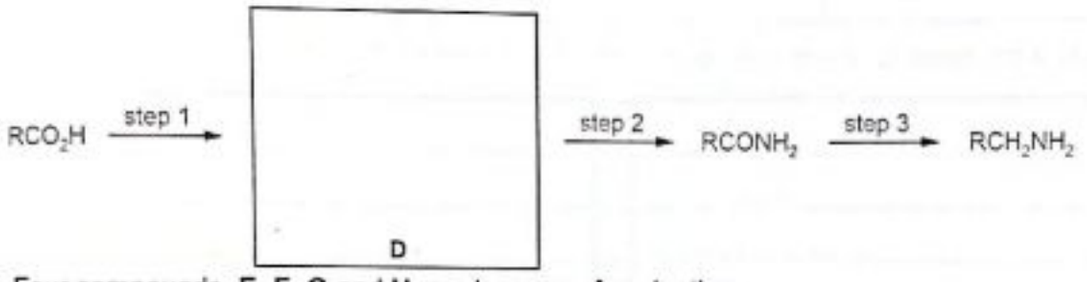
(ii) Suggest the reagents for

step 1.....

step 2.....

step 3.....

[2]



(b) Four compounds, **E**, **F**, **G** and **H**, are isomers of each other.
Each compound contains an aromatic ring and **two** functional groups from the following list.

- alcohol
- amide
- amine
- carboxylic acid
- ester
- phenol

(i) Which of these functional groups react readily with cold HC*l* (aq)?

..... **[1]**

(ii) Which of these functional groups react readily with cold NaOH(aq)?

..... **[1]**

The molecular formula of the four isomers, **E**, **F**, **G** and **H**, is $C_8H_9NO_2$. All four compounds are insoluble in water. **Table 1** shows their solubilities in acid or alkali.

compound	solubility in HC*l*(aq)	solubility in NaOH(aq)
E	insoluble	insoluble
F	soluble	soluble
G	soluble	insoluble
H	insoluble	soluble

(iii) Use this information to suggest the two functional groups, taken from the list on page 10, that each compound contains.

compound	first functional group	second functional group
E		
F		
G		
H		

(iv) Suggest a structure for each compound.

E

F

G

H

[4]